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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/807,556	07/30/2001	Susanna M. Rybak	15280-3711US	9130

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EXAMINER	
GEBREYESUS, KAGNEW H	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 01/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/807,556	RYBAK ET AL.	
	Examiner	Art Unit	
	Kagnew H Gebreyesus	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *15-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-3 and 5-14* is/are rejected.

7)☒ Claim(s) *4 and 8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse dated December 20, 2004 is acknowledged. Claims 1-14 are at issue and are present for examination. Claims 15-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to non-elected groups, there being no allowable or linking claims.

1. Although the polypeptides and the methods of selectively inhibiting growth of proliferating endothelial cells, the method of treating and the method of manufacturing a pharmaceutical composition comprising the polypeptide stem from a common concept and theory as argued by applicant each one is patentably distinct thus examining all the groups together is not agreed with. Each sequence, method of selective inhibition, treatment method and composition containing the RNases of the invention has to be thoroughly searched in sequence databases, non-patented and patent databases and the search for each is independent of the search required for the other which will cause an undue burden for examination. Therefor applicant's argument is not found persuasive because while the search necessary for examination of each group may overlap another, it is not coextensive and would become undue burden. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter as evidenced by their different classifications, restriction for examination purposes as indicated is proper and made FINAL.

Claim Objections

2. Claim 8 is objected to because of the following informalities: Claim 8 is objected to for using an abbreviation that is not defined the first time it is used. Appropriate correction is required.

Claim Rejections - 35 USC § 101

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 3, 5, 9-13 are rejected under 35 U.S.C. 101 because the claimed inventions are directed to non-statutory subject matter. In the absence of the hand of man, naturally occurring proteins and/or nucleic acids are considered non-statutory subject matter. *Diamond and Chakrabarty*, 206 USPQ 193 (1980). This rejection may be overcome by amending the claims to contain wording such as " An isolated and purified protein.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 1, 3, 5 and 8-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "an amino acid residue" in claim 1 (upon which claims 3, 5 and 8-14 depend) is followed by (SEQ ID NO:9), however SEQ ID NO: 9 does not represent one amino acid, it has at least 4-6 amino acid residues. Does X^3 represent all the 6 amino acid residues ? For examination purposes, the examiner has considered a single amino

acid residue in this position (X^3). This residue is an unknown amino acid residue in SEQ ID NO: 9 therefor will be considered one variable residue followed by the remaining part of an RNase A superfamily polypeptide selectively toxic to a proliferating endothelial cell. Claims 2, 4, 6 and 7 have not been included in this rejection as they recite further limitations which clarify the ambiguity in claim 1.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 5-7, 9-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an RNase polypeptide of SEQ ID NO: 2 and 4 does not reasonably provide enablement for any RNase polypeptide or any RNase polypeptide having 90% identity to an enzyme of SEQ ID NO: 2 and/or SEQ ID NO: 4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 1,3, 5-7, 9-14 are so broad as to encompass any RNase polypeptide or any RNase having 90% identity to an RNase polypeptide of SEQ ID NO: 2 or SEQ ID NO: 4. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides encoding RNase A broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence

and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only SEQ ID NO: 2 and SEQ ID NO: 4.

The proteins of SEQ ID NO: 2 and SEQ ID NO: 4 have RNase activity as well as a cytotoxic activity. The specification does not provide a method by which one of ordinary skill in the art may change upto 10% of the amino acids without changing the catalytic activity and the cytotoxic activity. While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all possible modifications and fragments of any RNase polypeptide with 90% identity to the RNase polypeptide of SEQ ID NOS: 2 or SEQ ID NO: 4 because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting RNase polypeptide activity; (B) the general tolerance of RNase polypeptide to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides

insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including RNase polypeptide with an enormous number of amino acid modifications of the RNase polypeptide of SEQ ID NOS: 2 and 4. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of RNase A having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 3, 5, 8-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Sakakibara et al., (1992) as evidenced by Griffith et al., (1997). Sakakibara et al., teach the isolation/purification of a unique RNase superfamily polypeptide, RNase UpI-2, from urine of pregnant women that include the additional N-terminal amino acid residues SLHV (serine, leucine, histidine and valine) in the coding sequence of the RNase superfamily polypeptide hEDN. In addition, functional characterization of the UpI-2 by it's catalytic activity, sensitivity

to inhibition by divalent cations and its immunoreactivity with antibodies to non-secretory RNase 1 indicates that RNase UpI-2 is a member of the RNase superfamily proteins. Furthermore, residues 1 to 4 and 5-20 of RNase UpI-2 show 100% identity to residues –4 to -1 of eosinophil-derived neurotoxin (EDN) and 1-16 of all the known non-secretory RNase (page 327 column 2). The cytotoxic effect of RNase UpI-2 on KS Y-1 cells is inherent to the protein as evidenced by Griffith et al. who isolated/purified the RNase polypeptide from the same source and demonstrated specific cytotoxic effects towards KS Y-1 cells.

9.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 2, 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sakakibara et al. in view of Barker et al. Barker et al., teach the complete sequence of human EDN of which the protein of Sakakibara et al., is a processing variant (see page 148 of Sakakibara et al.) and compare the polypeptide sequence of EDN and ECP (eosinophile cationic protein) polypeptides and show the putative signal peptide cleavage site for both proteins. Sakakibara et al., teach an RNase polypeptide that include residues SLHV (serine, leucine, histidine and valine) that are part of the signal sequence in the sequence disclosed by Barker et al. Including a methionine is routinely practiced for the purpose of recombinant production of proteins. The many advantages of recombinant production of useful proteins are well known within the art. These advantages include the ability to produce much larger quantities of the protein, being able to produce the protein in more easily handled organisms, reducing the number of steps necessary for the purification of a protein and producing the protein in a purer form by using an organism that does not include naturally occurring contaminants of the protein. Therefore, it would have been obvious to one of ordinary skill in the art to include a methionine residue for the purposes of recombinant production of the polypeptide.

Claim Rejections - 35 USC § 103

13. Claims 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sakakibara et al., (1992) in view of Griffith et al., (1997). Sakakibara et al., teach the isolation/purification of a unique RNase superfamily polypeptide, RNase UpI-2, from urine of pregnant women that includes additional N-terminal amino acid residues in the coding sequence of the RNase superfamily polypeptide hEDN. In addition, functional characterization of the UpI-2 by it's catalytic activity, sensitivity to inhibition by divalent cations and its immunoreactivity with antibodies to non-secretory RNase 1 indicates that RNase UpI-2 is a member of the RNase superfamily proteins. Furthermore, residues 1 to 4 and 5-20 of RNase UpI-2 show 100% identity to residues –4 to -1 of eosinophil-derived neurotoxin (EDN) and 1-16 of all the known non-secretory RNase (page 327 column 2). The cytotoxic effect of RNase UpI-2 on KS Y-1 cells is inherent to the protein as evidenced by Griffith et al., who isolated/purified the an RNase polypeptide from essentially the same source and demonstrated specific cytotoxic effects towards KS Y-1 cells. Griffith et al., did not test KS Y-3, KS 1, KS 2, KS 3, KS 4, KS 5 and KS 6 cells. However it would have been obvious for a person of ordinary skill in the art to examine the effects of the RNase on other Kaposi sarcoma cell lines to determine efficacy and/or specificity of cytotoxic activity.

Allowable Subject Matter

Claim 4 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The prior art does not suggest an additional glycine residue within the N-terminal MGSLHV sequence in any member of an RNase A superfamily polypeptide.

Furthermore the prior art provides no motivation for a skilled artisan to add a glycine residue to the N-terminus of the RNase of Sakakibara et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kagnew H Gebreyesus whose telephone number is 571-272-2937. The examiner can normally be reached on 8:30 am-5: 30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Achutamurthy ponnathapura can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kagnew Gebreyesus PhD.

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